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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BENHAM, Christopher, David [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). DAVIS, John [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). PARSONS, Andrew [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: GARRETT, Michael; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

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(54) Title: USE OF ANTAGONISTS OR PARTIAL AGONISTS OF THE VANILLOID RECEPTOR COMPLEXES FOR TREATING NEURODEGENERATIVE DISEASES

(57) Abstract

The use of antagonist or partial agonists of the vanilloid receptor complexes such as capsazepine or olvanil for the treatment of neurodegenerative diseases.

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USE OF ANTAGONISTS OR PARTIAL AGONISTS OF THE VANILLOID RECEPTOR COMPLEXES FOR TREATING NEURODEGENERATIVE DISEASES

The present invention relates to the use of antagonists or partial agonists of vanilloid receptors or vanilloid receptor complexes in the treatment or prophylaxis of neurodegenerative diseases.

Vanilloids are a class of natural and synthetic compounds which are characterised by the presence of a vanillyl group or a functionally equivalent group.

The term "vanilloid receptor or vanilloid receptor complex" is used herein to define a single protein or complex of more than one protein, or other components, whose function is modulated by a vanilloid compound.

A wide variety of vanilloid compounds of different structures have been disclosed in the literature, for example European Patent Specifications Nos. 347000 and 401903, UK Patent Specification No. 2226313, and PCT Patent Specification No. WO92/09285. Particularly notable examples of vanilloid compounds or vanilloid receptor modulators are capsaicin, namely trans 8-methyl-N-vanillyl-6-nonenamide, isolated from the pepper plant, capsazepine (Tetrahedron ,Vol 53,No 13,pp4791-4814 1997) and olvanil, N-(3-methoxy-4-hydroxy-benzyl)oleamide (J.Med. Chem. 1993, 36, 2595-2604).
The pharmacological effects of capsaicin and its vanilloid derivatives have been extensively studied and numerous proposals have been made in regard to possible therapeutic uses for the compounds including use as an analgesic or anti-inflammatory agent (GB 2226313). Such compounds have also been proposed for the treatment of herpes simplex infections (EP 347000) and respiratory diseases and disorders (EP 401903). The analgesic effect of capsaicin is characterised by an initial nociceptive effect from the compound but subsequently by an analgesic effect. Such effects can be blocked by capsazepine which acts effectively as an antagonist to the relevant capsaicin receptor. Another vanilloid compound, olvanil, acts as a partial antagonist/partial agonist.

We have now found that compounds which are antagonists (Walpole et al. 1994, J Med Chem 37: 1942-1954) or partial agonists (Janusz et al., 1993, J Med Chem 36: 2592-2604) for vanilloid receptors or vanillod receptor complexes (such compounds being hereinafter identified as compounds according to the invention) are capable of exerting a neuroprotective effect and are therefore useful in the treatment or prophylaxis of neurodegenerative diseases.

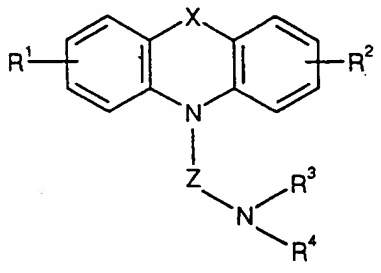
According to one feature of the present invention, we provide compounds according to the invention for use in the treatment or prophylaxis of neurodegenerative diseases.

According to a further feature of the present invention we provide the use of a compound according to the invention in the manufacture of a medicament for the treatment or prophylaxis of neurodegenerative diseases.

According to a still further feature of the present invention we provide a method for the treatment or prophylaxis of neurodegenerative diseases which comprises administering to a human subject an effective amount of a compound according to the invention.

The term "neurodegenerative disease " is used herein to denote a disease or disorder which is characterised by loss of cells which normally contribute to the structure and function of the central or peripheral nervous system. Examples of such diseases which may be treated in accordance with the invention include stroke, motor neurone disease, Parkinson's disease, Alzheimers disease, AIDS-related dementia , Lewy Body disease , brain or nerve injuries, peripheral neuropathies and prion disease.

Examples of compounds which may be employed in accordance with the invention include compounds of formula (I):



(I)

in which

R^1 and R^2, which may be the same or different, each represents hydrogen, C_{1-6} alkyl (e.g. methyl or ethyl), C_{1-6} alkoxy, halogen (e.g. chlorine) or trifluoromethyl;

X represents oxygen, sulphur, CH_2 or a chemical bond;

Z represents a C_{1-6} alkylene group;

R^3 and R^4, which may be the same or different, each represents hydrogen, C_{1-6} alkyl (e.g. methyl or ethyl) or R^3 and R^4 together with the adjacent nitrogen atom, form a 4- to 7-membered heterocyclic ring optionally containing one or more (e.g. 1, 2 or 3) further heteroatoms selected from oyxgen, nitrogen and sulphur, and optionally substituted for

example by one or more C_{1-6} alkyl (e.g methyl or ethyl) or hydroxy-C_{1-6} alkyl (e.g. 2-hydroxyethyl).

The group Z, which may be straight or branched, preferably contains three carbon atoms.

Examples of the above heterocyclic ring include pyrrolidino, piperidino , piperazino or morpholino.

Specific examples of compounds of formula (I) include:
10-[2-methyl-3-(pyrrolidin-1-yl)propyl]-10H-phenoxazine
10-[3-(dimethylamino)-2-methylpropyl]-2-methyl-10H-phenoxazine
10-[3-(dipropylamino)propyl]-10H-phenoxazine
2-chloro-10-[3-(pyrrolidin-1-yl)propyl]-10H-phenothiazine
10-(3-diethylaminopropyl)-10H-phenoxazine
10-[3-(4-methylpiperazin-1-yl)propyl]-10H-phenoxazine
10-[3-(diethylamino)-2-methylpropyl]-10H-phenoxazine
10-[3-(4-(2-hydroxyethyl)piperazin-1-yl)propyl]-10H-phenoxazine
2-ethyl-10-[2-methyl-3-(pyrrolidin-1-yl)propyl]-10H-phenoxazine
10-[3-(dimethylamino)-2-methylpropyl]-10H-phenoxazine

The above compounds may be prepared in accordance with the methods described by Schmolka et al, Synthesis, 1984, (1), 29-31 or by methods analogous thereto.

Particularly preferred examples of compounds for use in accordance with the invention include vanilloid compounds and especially capsazepine and olvanil referred to above. These compounds may be prepared in accordance with the processes disclosed in the above references.

For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound according to the invention and a physiologically acceptable carrier.

The compounds may be administered by any convenient method, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluoro-chlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 100 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the invention.

The physiologically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 2 and 200 mg, preferably between 50 mg and 150 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.2 mg and 20 mg, preferably between 0.5 mg and 5 mg, of the compound, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

Examples

Neuroprotective Effect against Glutamate-induced Cytotoxicity in HT-4 Cell Line

The neuroprotective effect of the above vanilloid compounds according to the invention is illustrated by the following investigation of the ability of the vanilloid compounds olvanil and capsazepine to protect the neuronal HT-4 cell line from glutamate induced cytotoxicity.

Cell viability was assayed using the MTT assay (Hansen, M.B., Nielsen, S.E. and Berg, K., Re-examination and further development of a precise and rapid dye method for measuring cell growth/cell kill, J. Immunol. Methods, 119 (1989) 203-210.) or by morphology. For MTT assays, cells were plated into 96-well plates at 5×10^3 cells/well in complete medium (DMEM/10%FCS/2mM glutamine), and 24hr later the experimental agents were added. Test compounds were added at the final concentration

shown in DMEM/10%FCS/2mM glutamine. Vehicles showed no effect at the dilutions used (data not shown) and glutamate was added to give a final concentration of 5mM. Cell viability was assessed by the ability of cells to reduce MTT, which was assayed a further 24hr after the addition of the experimental agents, according to the method of Hansen et al. Capsazepine and olvanil demonstrated a neuroprotective effect.

Neuroprotective Effect against Glutamate-induced Cytotoxicity in Rat Cortical Neurones

Cell viability was assayed using the MTT assay (Hansen et al. 1989), or by morphology. E16 rat primary cortical neurones were plated at $60x10^3$ cells/well in complete medium (DMEM:F12/5%HS/10%FCS/2mM glutamine). The cells were used within 48hr of plating. Test compounds were added at the final concentration shown in DMEM/10%FCS/2mM glutamine. Vehicles showed no effect at the dilutions used (data not shown). Cell viability was assessed by the ability of cells to reduce MTT, which was assayed a further 24hr after the addition of the experimental agents, according to the method of Hansen et al..Capsazepine demonstrated a neuroprotective effect

Protective effect for hippocampal slice cultures challenged with oxygen/glucose deprivation.

Organotypic hippocampal slice cultures were prepared according to Stoppini, L., Buchs, P.A. & Muller, D. A simple method for organotypic cultures of nervous tissue. J. Neurosci. Methods 37 (1991) 173-182. After 9-12 days the cultures were transferred to 6-well plates containing glucose-free medium, with or without agents to be tested, saturated with 95% N_2/5% CO_2 and placed in an anaerobic chamber, preequilibrated and maintained at 37°C, 100% humidity, 95% N_2/5% CO_2, for 45mins. The plates were then removed from the chamber and the cultures transferred to fresh serum-free medium containing 6microgram/ml propidium iodide and agent. The cultures were then placed back into the CO_2 incubator for 23hrs prior to analysis using NIH IMAGE 1.62. Capsazepine demonstrated a neuroprotective effect.

Claims

1. Antagonists or partial agonists for vanilloid receptor complexes for use in the treatment or prophylaxis of neurodegenerative diseases.

2. Capsazepine or olvanil for use as claimed in claim 1.

3. Compounds as claimed in claim 1 or claim 2 in which the neurodegenerative disease is stroke, motor neurone disease, Parkinsons disease, Alzheimers disease, AIDS-related dementia , Lewy Body disease , brain or nerve injuries, peripheral neuropathies and prion disease

4. The use of antagonists or partial agonists for vanilloid receptor complexes in the manufacture of a medicament for the treatment or prophylaxis of neurodegenerative diseases.

5. The use of capsazepine or olvanil as claimed in claim 4.

6. The use as claimed in claim 4 or claim 5 in which the neurodegenerative disease is as defined in claim 3.

7. A method for the treatment or prophylaxis of neurodegenerative diseases which comprises administering to a human subject an effective amount of an antagonist or partial agonist for vanilloid receptor complexes .

8. A method as claimed in claim 7 in which the said antagonist or partial agonist is capsazepine or olvanil .

9. A method as claimed in claim 7 or claim 8 in which the neurodegenerative disease is as defined in claim 3.

10. A pharmaceutical composition comprising an antagonist or partial agonist for vanilloid receptor complexes and a physiologically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Inter ɔnal Application No
PCT/EP 98/04005

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/165 A61K31/55 A61K31/645

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 20867 A (ACS GEZA ;ACS PETER (US); US GOVERNMENT (US); BIRO TAMAS (US); BLU) 22 May 1998 see abstract see page 1, line 1 - line 25; claims ---	1-3,10
X	WO 97 17077 A (OREAL ;LACHARRIERE OLIVIER DE (FR); BRETON LIONEL (FR)) 15 May 1997 see the whole document ---	1-3,10
X	EP 0 132 113 A (PROCTER & GAMBLE) 23 January 1985 see abstract; examples I,II,IV,V,VII see example VIII see page 17, line 18 - page 19, line 13; claims --- -/--	1-3,10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
19 November 1998	04/12/1998

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Inte .onal Application No
PCT/EP 98/04005

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication.where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 347 000 A (PROCTER & GAMBLE) 20 December 1989 cited in the application see abstract see page 4, line 31 - page 5, line 48 see page 8, line 44 - line 57; claims	1-3,10
X	WO 96 04915 A (EINSTEIN COLL MED ;DAVIES PETER (US); VINCENT INEZ J (US)) 22 February 1996 see abstract see page 12, line 24 - page 23, line 27 see page 28, line 13 - page 29, line 22; claims	1,3,4,6, 7,9,10
X	CHEMICAL ABSTRACTS, vol. 97, no. 25, 20 December 1982 Columbus, Ohio, US; abstract no. 207769, I. PLATONOV ET AL.: "EFFECT OF PHENOTHIAZINE DERIVATIVES ON THE DEVELOPMENT OF EXPERIMENTAL TRAUMATIC BRAIN EDEMA" XP002085074 see RNs 53-60-1, 58-33-3 and 60-99-1 see abstract & FARMAKOL. TOKSIKOL., vol. 45, no. 5, 1982, pages 42-45, MOSCOW	1,3,4,6, 7,9,10
A	G. ACS ET AL.: "TRIFLUOROPERAZINE MODULATES (3H)RESINIFERATOXIN BINDING BY HUMAN AND RAT VANILLOID (CAPSAICIN) RECEPTORS AND AFFECTS 45CA UPTAKE BY ADULT RAT DORSAL ROOT GANGLION NEURONES" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 274, no. 3, 1995, pages 1090-1098, XP002085071 see abstract see page 1093, right-hand column, paragraph 2	1,3,4,6, 7,9,10
X	US 4 833 138 A (OLNEY JOHN W) 23 May 1989 see abstract see column 2, line 44 - line 49 see column 3, line 16 - column 10, line 57; claims	1,3,4,6, 7,9,10

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INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/EP 98/04005

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DRAY A: "NEUROPHARMACOLOGICAL MECHANISMS OF CAPSAICIN AND RELATED SUBSTANCES" BIOCHEMICAL PHARMACOLOGY, vol. 44, no. 4, 18 August 1992, pages 611-615, XP000576776	1-3,10
Y	see the whole document	4-9
Y	RITTER ET AL.: "CAPSAICIN-INDUCED NEURONAL DEGENERATION IN THE BRAIN AND RETINA OF PREWEANLING RATS" JOURNAL OF COMPARATIVE NEUROLOGY, vol. 296, no. 3, 1990, pages 447-461, XP002085072 see the whole document	4-9
Y	M. UEDA ET AL.: "DETECTION OF CAPSAICIN-EVOKED RELEASE OF GLUTAMATE FROM SPINAL DORSAL HORN SLICES OF RAT WITH ON-LINE MONITORING SYSTEM" NEUROSCIENCE LETTERS, vol. 155, no. 2, 1993, pages 179-182, XP002085073 see the whole document	4-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/04005

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7-9
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 7-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
SEE FURTHER INFORMATION SHEET PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds which are theoretically contained within the definition "antagonists or partial agonists for vanilloid receptor complexes" the search had to be restricted on economic grounds to the general idea of the invention and to the compounds mentioned on page 3, lines 9-20 and in the examples (Art. 6 PCT; Guidelines Part B, Chapt. II.7 last sentence and Chapt. III, 3.7).

Claims searched completely: 2, 5, 8
Claims searched incompletely: 1, 3, 4, 6, 7, 9, 10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/04005

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9820867 A	22-05-1998	AU 5460598 A	03-06-1998
WO 9717077 A	15-05-1997	FR 2740682 A	09-05-1997
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